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Diabetes Mellitus and Right Ventricular Dysfunction in Heart Failure with Preserved Ejection Fraction

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Running title: Diabetes mellitus and RV dysfunction in HFpEF

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ABSTRACT

Diabetes mellitus is associated with left-sided myocardial remodeling in heart failure with preserved ejection fraction (HFpEF). Little is known about the impact of diabetes mellitus on right ventricular (RV) function in HFpEF. We therefore studied the relation between diabetes mellitus and RV dysfunction in HFpEF. We have examined HFpEF patients who underwent simultaneous right heart catheterization and echocardiography. RV *systolic* function was assessed using multiple established echocardiographic parameters and systolic dysfunction was present if ≥ 2 parameters were outside the normal range. RV *diastolic* function was assessed using the peak diastolic tricuspid annular tissue velocity (RV e') and present if < 8.0 cm/s. Diabetes mellitus was defined as documented history of diabetes, fasting glucose ≥ 7.0 mmol/L, positive glucose intolerance test or glycated hemoglobin $\geq 6.5\%$. A total of 91 patients were studied; mean age 74 ± 9 years; 69% women. A total of 37% had RV systolic dysfunction and 23% RV diastolic dysfunction. 37% of the patients had type 2 diabetes mellitus. These patients had higher pulmonary artery pressure (34 vs. 29 mmHg, $p=0.004$), more RV systolic dysfunction (57 vs. 29%, $p=0.009$), more RV diastolic dysfunction (46 vs. 12%, $p=0.001$) and lower RV e' (8.7 vs. 11.5 cm/s, $p=0.006$). The presence of diabetes mellitus was independently associated with RV *systolic* dysfunction [OR 2.84 (1.09-7.40) $p=0.03$] and with RV *diastolic* dysfunction [OR 4.33 (1.25-15.07) $p=0.02$], after adjustment for age, sex and pulmonary pressures. In conclusion, diabetes mellitus is strongly associated with RV systolic and diastolic dysfunction in patients with HFpEF, independent of RV afterload.

Diabetes mellitus is a common comorbidity in patients with heart failure with preserved ejection fraction (HFpEF),(1,2) and is independently associated with increased morbidity and mortality.(2,3) Right ventricular (RV) dysfunction is also highly prevalent in HFpEF, is associated with a poor prognosis and is an important target for therapy in patients with HFpEF.(4-6) The exact mechanisms underlying the development of RV dysfunction in HFpEF are unclear and probably multifactorial, but an important determinant is pulmonary vascular disease resulting in pulmonary hypertension (PH).(7-9) Previous studies in individuals without heart failure have demonstrated that diabetes mellitus was associated with structural and functional remodeling of the RV.(10-12) Therefore, it can be speculated that in HFpEF the RV may also be affected by diabetes mellitus. More insight into these mechanisms may help to develop treatment strategies that target the right heart in HFpEF. We therefore sought to investigate the relation between diabetes mellitus and RV dysfunction in patients with HFpEF – with and without diabetes mellitus – who underwent simultaneous cardiac catheterization and echocardiography.

METHODS

The study cohort is previously described in detail.(7) In brief, 102 patients with HFpEF with LV ejection fraction $\geq 45\%$ and New York Heart Association (NYHA) functional class $\geq II$ were identified. These patients had echocardiographic signs of increased right-sided pressures and were therefore referred for left and right heart catheterization for evaluation of PH. Additional inclusion criteria for the present study were LV diastolic dysfunction ($E/e' \geq 13$ or mean e' septal and lateral wall < 9 cm/s) and/or left atrial (LA) dilatation (LA volume index ≥ 34 mL/m² or LA parasternal diameter ≥ 45 mm) and/or N-terminal of the pro-hormone brain natriuretic peptide (NT-proBNP) ≥ 125 ng/L.(13) Patients were excluded if there was no simultaneous echocardiographic assessment available. In addition, patients in whom RV

function could not be assessed reliably on echocardiography using at least two recommended parameters reflecting RV systolic function,(14) were excluded as well.

Patients underwent a physical examination and laboratory testing, including glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR) and N-terminal of pro-B type natriuretic peptide (NT-proBNP). eGFR was calculated using the Modification of Diet in Renal Disease equation.

Diabetes mellitus was defined as a documented history of diabetes, fasting plasma glucose ≥ 7.0 mmol/L, plasma glucose ≥ 11.1 mmol/L two hours after the oral glucose dose or HbA1c $\geq 6.5\%$ (≥ 48 mmol/L).(15) Renal dysfunction was defined as eGFR < 60 ml/min/kg.

All patients included in the present study underwent left and right heart catheterization performed by a single experienced interventional cardiologist (E.S.H.). The invasive hemodynamic protocol used in our center is previously described in detail.(16) In brief, invasive measurements were performed with the patient in fasting state and in supine position. First, the system was zeroed at patients' heart level. A 7F thermodilution balloon-tipped catheter was inserted through the femoral vein and advanced through the right atrium and RV into the pulmonary artery and wedge position. RV end-diastolic pressure, pulmonary artery pressures (PAP) and pulmonary capillary wedge pressure were obtained at end-expiration. Left heart catheterization was performed to exclude significant coronary artery disease or left-sided valve disease and LV end-diastolic pressure was measured. Cardiac output was calculated according to Fick. Pulmonary vascular resistance was subsequently calculated and expressed as dynes \cdot sec \cdot cm $^{-5}$ and pulmonary arterial compliance was calculated using the volume method.(17)

Echocardiographic images were acquired simultaneous with the cardiac catheterization using a Vivid S6 system (General Electric, Horton, Norway) using a 2.5- to 3.5-mHz probe. Analyses were independently performed by two blinded experienced investigators using GE

EchoPAC version BT12. Digitally stored images were used to measure the tricuspid annular plane systolic excursion (TAPSE) in M-mode on the apical 4-chamber view. In addition, both the peak *systolic* tissue velocity of the lateral tricuspid annulus (RV s') and the peak *diastolic* tissue velocity of the lateral tricuspid annulus (RV e') were assessed (**Figure 1**). RV fractional area change (FAC) using the apical 4-chamber view were assessed, according to current recommendations.(14) Finally, RV free wall longitudinal speckle-tracking strain was assessed as previously described with good inter- and intra-observer variability.(18) Each parameter was measured in duplicate at two time points and averaged to obtain one single value. Right ventricular *systolic* dysfunction was defined when at least two parameters for RV systolic function were below the lower recommended limit of normal (i.e. TAPSE <17 mm, RV s' <9.5 cm/s, RV FAC <35% and/or RV free wall longitudinal strain > -20%).(14) RV diastolic dysfunction was defined as RV e' <8.0 cm/s.(19) Finally, RV Tei-index (i.e. RV index of myocardial performance) was calculated using the tissue Doppler method (i.e. isovolumetric time minus isovolumetric relaxation time, divided by total RV ejection time), as illustrated in **Figure 1**.(14)

Data is described as mean \pm standard deviation, median [25th-75th percentile] or numbers (percentages). Differences in continuous variables between two groups were tested using independent samples t-test or Mann-Whitney U-test, according to distribution. Differences in categorical variables between two groups were calculated using Chi-squared tests. Linear regression models were performed to test correlations between continuous variables. Unadjusted and adjusted analyses for the association between diabetes mellitus with the presence of RV systolic and diastolic dysfunction were performed using binary logistic regression models. In multivariable logistic regression analyses, the association between diabetes mellitus and RV systolic and diastolic dysfunction was adjusted for relevant covariates (i.e. age, sex, comorbidities, mean PAP, PVR and LV systolic and diastolic function). Due to

the small study sample, multiple logistic regression analyses were performed with no more than 3 adjustment variables each. In addition, HbA1c (%) was correlated with the presence of RV systolic and diastolic dysfunction using binary logistic regression and odds ratios (OR) were depicted per standard deviation increase in HbA1c. Statistical significance was considered achieved with p-value <0.05 and all analyses were performed using SPSS (Version 23, 2015).

RESULTS

Of the initial population of 102 patients with HFpEF, 4 patients did not undergo simultaneous echocardiography and heart catheterization and were therefore excluded. Another 7 patients were excluded because echocardiographic quality was insufficient for reliable assessment of RV systolic function. Therefore, a total of 91 patients were included in the present study. Characteristics of the population are described in **Table 1**. A total of 34 patients (37%) had type 2 diabetes mellitus and 6 of these patients had new onset diabetes with HbA1c $\geq 6.5\%$ at the time of assessment. As seen in **Table 1**, patients with diabetes had higher body mass index and more often coronary artery disease, compared to HFpEF patients without diabetes. The former group of patients also had higher serum creatinine concentrations and lower eGFR. HFpEF patients with diabetes mellitus were also more symptomatic, as evidenced by more diuretic usage, higher NYHA functional class and lower percentage of predicted peak VO_2 .

The echocardiographic and cardiac catheterization measurements are summarized in **Tables 2** and **3**. Right ventricular peak diastolic tissue velocity could be assessed in 83 patients (91%), and 19 of these (23%) had RV diastolic dysfunction (i.e. RV $e' < 8.0$ cm/s). **Figure 2** illustrates the correlation between left- and right-sided peak diastolic tissue velocities. RV e' was correlated with both LV lateral e' (**Figure 2A**) and septal e' (**Figure 2B**).

Patients with diabetes mellitus more often had RV systolic and diastolic dysfunction, compared to non-diabetic individuals (**Table 2**). In addition, RV end-diastolic pressure and mean PAP were higher in HFpEF patients with diabetes mellitus, compared to patients without

diabetes mellitus, while PVR was not significantly different between both groups (**Table 3**). In non-ischemic HFpEF (with exclusion of patients with coronary artery disease), RV systolic dysfunction remained more prevalent in patients with diabetes mellitus compared to those without (53 vs. 21%, respectively, $p=0.02$).

In the logistic regression model (**Table 4**), diabetes mellitus was significantly associated with the presence of both RV *systolic* and *diastolic* dysfunction, after adjustment for all relevant covariates. As seen in **Table 4**, diabetes mellitus was also associated with higher RV end-diastolic pressure, independent of these covariates, except for mean PAP.

In addition, higher levels of HbA1c (%) were also associated with RV systolic dysfunction (OR 1.88 [1.12-3.18] $p=0.02$) and RV diastolic dysfunction (OR 1.81 [1.06-3.10] $p=0.03$), although there was also a strong correlation between HbA1c and the presence of diabetes mellitus ($\beta=0.61$, $p<0.001$).

In the present cohort, 25 patients (27.5%) had $PVR >240$ dynes/s/cm⁻⁵ and 13 (52%) of these patients had diabetes mellitus. In a secondary analysis in this subgroup of patients with high PVR, the patients with diabetes mellitus had more RV systolic dysfunction (85 vs. 42%, respectively, $p=0.03$), lower RV e' (7.4 vs. 11.5 cm/s, respectively, $p<0.001$) and more RV diastolic dysfunction (67 vs. 0%, $p<0.001$), compared to the 12 patients without diabetes mellitus. Pulmonary vascular resistance was comparable in this subgroup between patients with and without diabetes mellitus (331 vs. 347 dynes/s/cm⁻⁵, respectively, $p=0.44$).

DISCUSSION

The present study demonstrated that RV *systolic* dysfunction was present in 37%, and RV *diastolic* dysfunction in 23% of HFpEF patients. Diabetes mellitus was strongly associated with both RV systolic and RV diastolic dysfunction, independent of RV afterload. To our knowledge, these findings are novel and add to the knowledge about the development of RV dysfunction in patients with HFpEF.

The observation that RV systolic dysfunction is prevalent in HFpEF, is in line with a large number of previous studies performed in patients with HFpEF and is strongly related to PH-HFpEF.(4,9) In a previous study, Gan *et al.* observed that RV diastolic function is impaired in patients with PH, and RV diastolic dysfunction could improve by reducing RV afterload with sildenafil.(20) Thus, RV diastolic dysfunction in HFpEF may also be related to longstanding increased afterload in the setting of PH-HFpEF. Interestingly, we observed that the presence of diabetes mellitus was also associated with both RV systolic and diastolic dysfunction in patients with HFpEF. There is evidence that comorbidities (including diabetes mellitus) contribute to endothelial dysfunction via release of inflammatory cytokines, increased levels of reactive oxygen species and decreased availability of nitric oxide.(21) Longstanding exposure to this oxidative stress and systematic inflammation in the setting of comorbidities are important mechanisms of the development of adverse myocardial remodeling and left ventricular diastolic dysfunction is one of its first manifestations.(21) Recently, Lindman *et al.* showed that HFpEF patients with diabetes mellitus indeed had a more severe phenotype of HFpEF, with increased risk of hospitalization, more advanced LV hypertrophy and higher concentrations of biomarkers that relate to oxidative stress, inflammation and fibrosis.(2) In the present study, we observed that HFpEF patient with diabetes had a higher prevalence of ischemic heart disease, higher use of diuretics and lower glomerular filtration rate. Nephropathy is an ominous sign in patients with diabetes, and is strongly associated with cardiac ischemia and diabetic cardiomyopathy.(22) Diabetic nephropathy may also have an important adverse impact on both ventricles simultaneously.

Previously, Karamitsos *et al.* investigated RV diastolic function in young individuals with type I diabetes mellitus. These individuals without heart failure and no evidence of coronary artery disease or hypertension had higher transtricuspid E/A ratio and lower tricuspid annular e', compared to healthy controls.(23) This suggests that, similar as for the LV, RV

diastolic dysfunction seems also an early sign of myocardial remodeling in diabetes mellitus. Also in patients with pulmonary arterial hypertension, diabetes mellitus is associated with reduced RV work load and lower survival rate, compared to non-diabetic individuals with pulmonary arterial hypertension.(24) In the present cohort in the subgroup of patients with high PVR, the patients with diabetes mellitus also had more RV systolic and diastolic dysfunction, while PVR was similar between both groups.

Besides a direct myocardial effect, chronic hyperglycemia may also have an effect on pulmonary vascular remodeling ultimately resulting in right-sided pressure overload. For instance, Berthelot *et al.* included diabetes mellitus to a clinical risk model for the presence of PH in HFpEF.(25) We have recently shown that diabetes mellitus is more prevalent in HFpEF patients with combined post- and pre-capillary PH than in HFpEF patients with isolated post-capillary PH.(7) In these patients, diabetes mellitus might enhance adverse pulmonary vascular disease through increased inflammation and reduced vasodilatation.(26) This hypothesis is supported by the fact that acute hyperglycemia (to glucose levels of 16.7 mmol/l) impairs endothelium-dependent vasodilation and lowers nitric oxide and prostacyclin in healthy, non-diabetic individuals.(27)

A hyperglycemic state could also be a plausible target for future treatment options. The phosphodiesterase type 5A inhibitor vardenafil, which enhances the vasodilator effects of cyclic guanosine monophosphate, was tested in Zucker diabetic fatty rats.(28) In this animal model, vardenafil was reported to prevent the development of diabetes mellitus-associated myocardial remodeling, defined as increased myocardial stiffness and worsened diastolic dysfunction.(28) Further studies are needed to investigate whether there is a role for such therapies to prevent the onset and/or worsening of RV dysfunction in diabetic HFpEF patients.

There are several limitations that need to be addressed. First, the sample size was small, thus we were not able to investigate extensive multivariable associations of comorbidities with

RV dysfunction. Second, patients with suspected PH on previous echocardiography were referred for invasive evaluation of PH. This resulted in a selection bias with potential overrepresentation of PH-HFpEF. The results may therefore not be applicable to the entire HFpEF population. Furthermore, established methods to investigate RV diastolic dysfunction are lacking. In the present study, invasive pressure-volume loops were not obtained and also transtricuspid inflow (i.e. E/A ratio) was not available. Therefore, we could only measure RV diastolic function using the tricuspid annular tissue velocity and RV end-diastolic pressure.

Conflict of interest: **C.S.P.L.** reports support from Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Medtronic, and Vifor Pharma; and has consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca, and Janssen Research & Development, LLC, outside the submitted work. **A.A.V.** has received board memberships and/or travel expenses from Novartis, Servier, and Bayer for participation in studies in the field of HFpEF, outside the submitted work. **E.S.H.** has received an unrestricted Investigator Initiated Research Grant from Pfizer Global Pharmaceuticals, not related to the present work. **D.J.V.V.** has received Board Memberships and/or travel expenses from Novartis and Corvia Medical for participation in studies in the field of HFpEF, not related to the present work. All other authors report no conflict of interest.

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FIGURE LEGENDS

Figure 1: Echocardiographic assessment of right ventricular tissue velocities and Tei-index.

Right ventricular (RV) Tei-index is assessed using the tissue Doppler method by measuring the total tricuspid valve closure to opening time (T_a) and right ventricular ejection time (T_b). Tissue Doppler echocardiography is also used to assess the peak systolic tissue velocity (RV s') and peak diastolic tissue velocity (RV e') of the lateral tricuspid annulus.

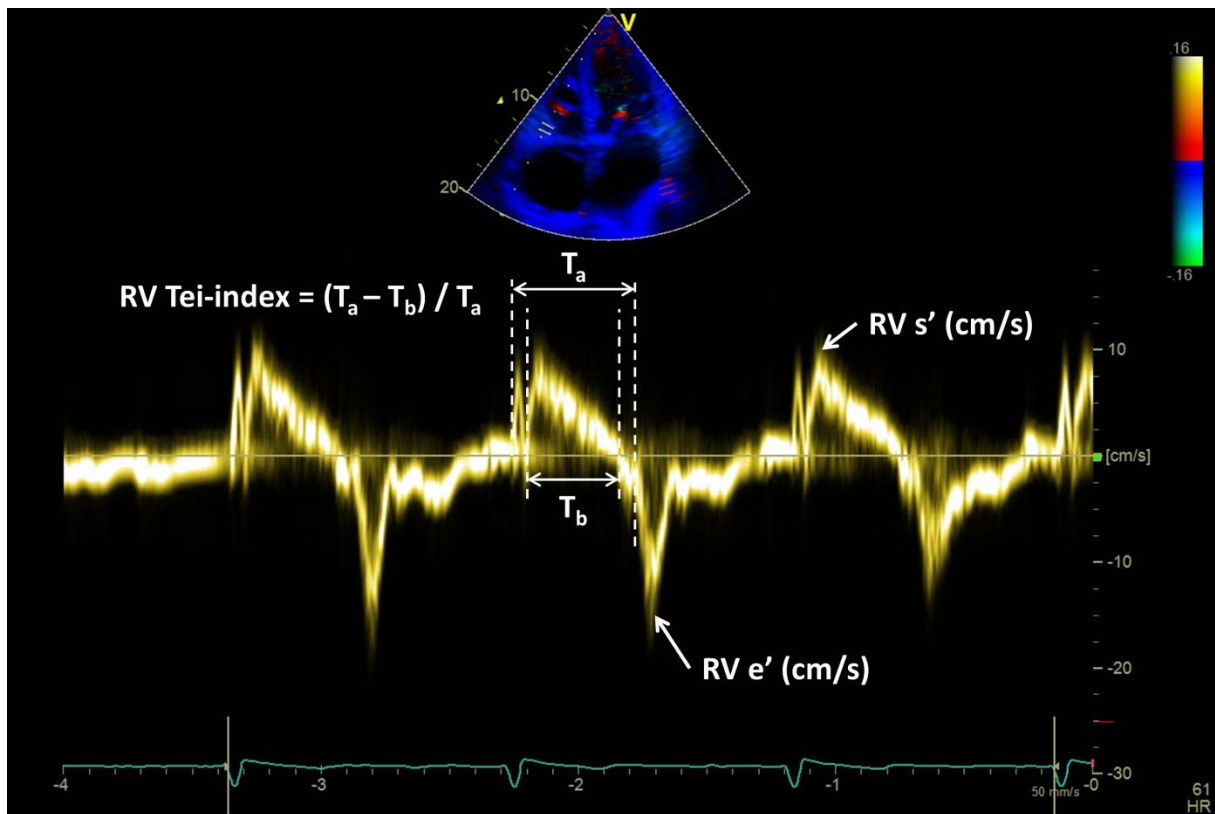


Figure 2: Left and right ventricular diastolic dysfunction. Figure 2A: Correlation between peak diastolic tissue velocity near the lateral mitral valve annulus, with the peak diastolic tissue velocity near the lateral tricuspid valve annulus. **Figure 2B:** Correlation between peak diastolic tissue velocity of the basal septal wall, with the peak diastolic tissue velocity near the lateral tricuspid valve annulus.

